A NOTE ON THE EFFECT OF DUODENAL EXTRACT AND OF HEXOESTROL ON THE ANTI-INSULIN ACTIVITY OF ANTERIOR LOBE PITUITARY EXTRACT.

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(One Text-figure.)

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De Barbieri (1939) has claimed that pretreatment with a duodenal extract, administered orally, will abolish the well-known chronic insensitivity to insulin induced by injection of anterior lobe pituitary extract (see Young, 1938). However, Loew, Gray and Ivy (1940) conclude that the duodenum plays little part in carbohydrate metabolism, but fail to consider De Barbieri's work. Consequently it is of interest to investigate De Barbieri's claim.

As recent work (James and Nelson, 1940; Griffiths, Marks, and Young, 1941; Ingle, 1941) has shown that synthetic oestrogens exert a profound influence on carbohydrate metabolism, it was also considered of interest to study the effect of injection of a synthetic oestrogen, hexoestrol, on anterior pituitary induced insulin insensitivity. The results of some experiments on both the effect of duodenal extract and of hexoestrol on this insulin insensitivity are recorded below.

Acknowledgement.

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Methods.

Biological.—Male and female rabbits on a régime of bran and lucerne were used for the study of the effect of duodenal extract on glycotropic activity of pituitary extract. Each rabbit served as its own control. Four experiments were made using freshly-prepared extracts each time.

In the hexoestrol experiments, male wistar rats were used. These were given a standard laboratory diet, fresh milk, and water, daily.

Chemical.—The duodenal extract used was made from fresh ox duodenal mucosa according to Heller (1929), and the pituitary extract from fresh anterior lobes of ox pituitaries by a modification of the method of Young (1938). These two extracts were injected subcutaneously. The hexoestrol was dissolved in arachis oil and injected intraperitoneally. Burroughs Wellcome's crystalline insulin was used in all experiments. Details of the injections are given in Table 1 and in the legends to Figure 1.

In the rabbit experiments, two control venous blood samples were taken before the intravenous injection of two units of insulin, and blood samples at 10, 20, 30, 60, 90 and 150 minutes after this injection. In the rat experiments blood was obtained by decapitation, 1 hour after subcutaneous injection of one unit of insulin.

Blood sugar was determined by the method of Hagedorn and Jensen on 0·1 ml. blood.

Results.

From Figure 1, curves A and B, it is seen that chronic insensitivity to the hypoglycemic effect of 2 units of insulin injected intravenously, is induced by injections of anterior lobe pituitary extract given some hours previous to the insulin, and that injections of duodenal extract do not have any effect on this insensitivity. Curve C shows the normal response to the intravenous injection of 2 units of insulin.

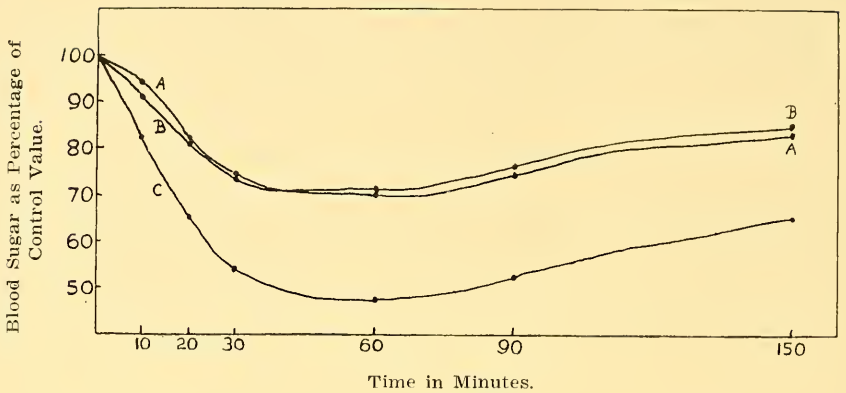

Fig. 1.

Curve A.—Rabbits 1, 2, 3 and 4. Average response, at conclusion of 21-hour fast, to 2 units of insulin injected intravenously, after pretreatment with 4·5 c.c. of anterior lobe pituitary extract at 0 and 17 hours.

Curve B.—Same rabbits. Average response, at conclusion of 21-hour fast, to 2 units of insulin injected intravenously, after pretreatment with 4·5 c.c. of anterior lobe pituitary extract and 15·0 c.c. of duodenal extract at 0 and 17 hours.

Curve C.—Same rabbits. Average response, at conclusion of 21-hour fast, to 2 units of insulin, injected intravenously. No pretreatment.

The results of the experiments with hexoestrol are summarized in Table 1. From this table it is seen that in rats untreated with hexoestrol, the anterior pituitary extract produced a definite inhibition of the hypoglycemic action of the insulin, the blood sugar

Table 1.

Number of Rats in Group.	Average Wt., grams.	Treatment. 4 Days' Pretreatment.	Treatment. 5th Day. A.	Treatment. 5th Day. B.	Blood Sugar in mgm. % 1 Hour after Final Injection.
5 (control group)	277	1 c.c. arachis oil daily, injected intraperitoneally.	1 c.c. H_2O injected intraperitoneally at 0, 2 and 4 hours during 6-hour fast.	0·5 c.c. H_2O injected subcutaneously at 6th hour of fast.	106
5	255	1 c.c. arachis oil daily, injected intraperitoneally.	1 c.c. of anterior pituitary extract injected intraperitoneally at 0, 2 and 4 hours during 6-hour fast.	1 unit insulin in 0·5 c.c. H_2O subcutaneously at 6th hour of fast.	77
5	225	2·5 mgm. hexoestrol daily, in 1 c.c. arachis oil, injected intraperitoneally.	1 c.c. of anterior pituitary extract injected intraperitoneally at 0, 2 and 4 hours during 6-hour fast.	1 unit insulin in 0·5 c.c. H_2O subcutaneously at 6th hour of fast.	56
5	240	1 c.c. arachis oil daily, injected intraperitoneally.	1 c.c. H_2O injected intraperitoneally at 0, 2 and 4 hours during 6-hour fast.	1 unit insulin in 0·5 c.c. H_2O subcutaneously at 6th hour of fast.	46
4	204	2·5 mgm. hexoestrol daily, in 1 c.c. arachis oil, injected intraperitoneally.	Fasted for 6 hours.	1 unit insulin in 0·5 c.c. H_2O intraperitoneally at 6th hour of fast.	49
4	189	1 c.c. arachis oil daily, injected intraperitoneally.	Fasted for 6 hours.	1 unit insulin in 0·5 c.c. H_2O intraperitoneally at 6th hour of fast.	50

falling to an average value of 77 mgm. %, whilst in untreated rats injected with insulin the blood sugar fell to 46 mgm. %. The figure for the control group of rats was 106 mgm. %. However, in the rats pretreated with hexoestrol, the inhibition of insulin hypoglycemia due to pituitary extract was largely overcome, and the blood sugar value fell to a mean of 56 mgm. %. By Fisher's t-test the difference between the mean value 56 mgm. % and the mean value of 77 mgm. % for the pituitary treated group without hexoestrol pretreatment, was found to be significant ($\rho = 0{\cdot}05$).

It is also apparent from the last two experiments in Table 1 that hexoestrol does not inhibit the anti-insulin activity of the pituitary extract by increasing the animal's sensitivity to insulin *per se*. It is possible, then, that hexoestrol inhibits the action of anterior pituitary extract by retarding its absorption from the peritoneal cavity. This is unlikely, as in these last two experiments in Table 1 the insulin was injected intraperitoneally and the hexoestrol apparently had no effect on its absorption, so there is no reason to suppose that hexoestrol alters the absorption of anterior pituitary extract.

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